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VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/215,077	12/18/98	PRICE	P 23070-086711

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EXAMINER	
NGUYEN, B	
ART UNIT	**PAPER NUMBER**
1641	5

DATE MAILED: 02/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/215,077	Price et al
Examiner	**Group Art Unit**
Bao-Thuy L. Nguyen	1641

☒ Responsive to communication(s) filed on *12/18/98* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3 & 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Sequence Disclosures

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a) (1) and (a) (2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply with Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is required to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821 (g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Priority

2. The subject matter of claims 1-8, i.e. correlation of elevated levels of YKL-40 to cirrhosis of the liver, first appeared in PCT/US96/07754, filed 8 July 1994; therefore claims 1-8 receive the benefit of that filling date, and not that of parent application serial number 08/089,989.

3. The status of the parent applications needs to be updated on the first page of the specification.

Information Disclosure Statement

4. The information disclosure statement filed 1/25/00 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information. References A33-A36 appear to be listing of sequences, however, no explanation as to how these sequences are relevant to the instant application. It has been placed in the application file, but the information referred to therein has not been considered.

Drawings

5. Formal drawings have been received and are acceptable.

Claim Rejections - 35 USC § 112

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening for the presence of a generic disease state which is associated with degradation of connective tissue containing YKL-40, does not reasonably provide enablement for the identification of specific diseases, such as cirrhosis of the liver. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention - the invention is directed toward the identification of a circulating protein associated with extracellular fiber matrix metabolism in mammalian connective tissues. Specifically, it is directed to assays for the detection and quantitation of molecules and fragments of YKL-40.

The state of the prior art - Applicant's post-filing publication, i.e. Johansen et al., (Brit. J. Rheum. 31:949, 1993), equates YKL-40 with a protein found in synovial cells by Nyirkos et al (Biochem. J. 268:265, 1990). Nyirkos et al teach that according to the N-terminal sequence of the protein, that "this protein is the human homologue of a bovine [mammary] protein isolated from non-lactating cows" (see page 267, column 2, discussion), and Applicant's own discussion states that YKL-40 has been discovered to be elevated in patients with a metastasis of breast

cancer cells and persons with join diseases including rheumatoid arthritis and osteoarthritis. The prior art is silent on the correlation between elevated level of YKL-40 in samples such as blood, plasma and serum, and cirrhosis of the liver.

The predictability or lack thereof in the art - as indicated by the prior art, YKL-40 has not been definitely linked to one specific disease nor has a particular amount been shown to be indicative of one disease over another. While it is possible to screen for the presence of a disease state which is associated with degradation of connective tissue, by detecting elevation in the level of YKL-40 as compare to normal level, it has not been possible to identify one particular diseased stated, e.g. cirrhosis of the liver, as indicated by the elevation of YKL-40.

The amount of direction or guidance present - appropriate guidance is provided by the specification to screen for the presence of the degradation of connective tissue by detecting elevated levels of YKL-40. However, no guidance is available to teach a skilled artisan how to identify the presence of cirrhosis of the liver by the elevation of YKL-40.

Ex. 10

The presence or absence of working examples - one working example is provided indicating that YKL-40 level is elevated in patients with alcoholic cirrhosis as compare to patients with normal liver functions. However, other examples are also present showing that elevated YKL-40 levels are also detected in patients with rheumatoid arthritis or other joint disease and in those with breast cancer. Thus, the instant specification further demonstrates that YKL-40 level cannot be related to one specific disease; rather, it is indicative of a disease state associated with degradation of connective tissue containing YKL-40.

The quantity of experimentation necessary - It would be undue experimentation for a skilled artisan to make and use the invention as claimed.

The relative skill of those in the art - the level of skill in the art is high.

The breadth of the claims - the instant claim is directed toward a method identifying the presence of cirrhosis of the liver in a mammal by comparing the measured level of YKL-40 in a biological sample to that of a normal, healthy mammal, wherein a statistically significant difference indicates the presence of cirrhosis.

Elevation of YKL-40 in a patient can be due to a number of different diseases, and no particular amounts have been shown to be indicative of one disease over another; therefore, while it may be possible to screen for a generic disease state, it is not possible to identify the presence of any specific disease, e.g. cirrhosis of the liver, by measuring the amount of YKL-40 as claimed. Even the specification teaches that "[b]ecause in certain instances serum YKL-40 may stem from sources other than the tissue of interest, a sample should, if possible, be taken from the tissue of interest" (specification, page 26, lines 11-13), and "..serum levels of YKL-40 can ...be related to the incidence of joint disease..however, distinctions between the different join diseases evaluated are not apparent..." (specification, page 38, lines 11-13).

In view of the teachings of *In re Wands*, 8 USPQ2d 1400, it has been determined that the level of experimentation required to correlate an elevation in the level of YKL-40 to the presence of cirrhosis of the liver are undue. It has been set forth above that 1) the experimentation required to measure and correlate the elevation in the level of YKL-40 to the presence of cirrhosis of the liver would be great as 2) there are experiments provided that indicate that the elevation in the level of YKL-40 is indicative of a more generic disease state associated with degradation of connective tissues, instead of a specific disease such as cirrhosis of the liver, 3) there are no proper guidance for how to distinguish between one degenerative disease from another using the elevation in YKL-40 in the instant specification, 4) the nature of the invention is a correlation between an elevated level of YKL-40 in a biological sample as compare to that of a normal, healthy mammal and the presence of cirrhosis, 5) the relevant skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by Johansen et al and Nyirkos et al, described above, and lastly 7) the claims broadly recite a method to identify the presence of cirrhosis of the liver by comparing the measured level of YKL-40 in a sample with those of a normal sample, wherein a statistically significant difference indicates the presence of cirrhosis without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of skill in the art could not make and use the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyirkos et al (Biochem. J. 268:265, 1990) or Johansen et al (J. Bone Min. Res. 7(5):501, 1991) each in view of Maurer et al (Meth. Enz., 70:49, 1980).

Nyirkos et al teach the detection and quantitation of a 39 kD protein (Applicants' own publication, i.e. Johansen et al. (J. Bone Min. Res., 7(5):501, 1991), equates YKL-40 with the protein of Nyirkos et al (see page 507, column 2, lines 9-11) from synovial cells derived from the tissue of osteoarthritic and rheumatoid arthritis patients undergoing joint replacement (page 269,

column 1). Nyirkos et al suggest that the protein could be useful as a marker distinguishing the synovial cell from fibroblasts. (See page 269, column 2, discussion, last paragraph).

Nyirkos et al differ from the instant invention in that they do not specifically teach the use of polyclonal or monoclonal antibodies as a means to measure YKL-40.

Johansen et al teach that a complete understanding of the physiologic function of a given cell requires knowledge of the identity and amount of each protein secreted by that cell. One of two methods to assess these proteins is an immunological assay for antigens (see page 501, Introduction). Johansen et al were able to detect and quantitate a new protein, YKL-40, from human osteosarcoma cells in SDS gels (see page 507, column 1, top).

Johansen et al differs from the instant invention in that they do not specifically teach the use of polyclonal or monoclonal antibodies as a means to measure YKL-40.

Maurer et al teach that antibodies can be prepared against virtually any macromolecule (page 50, second full paragraph), that polyclonal antibodies can be produced via immunization of a mammal (page 51, under "animal Species"), and that monoclonal antibodies can be produced from hybridomas (pages 65-67). Maurer et al further teach the many utilities of monoclonal and polyclonal antibodies, such as detection and assaying or concentrating and purifying an antigen of interest (page 49).

It would have been obvious to one of ordinary skill in the art to use either polyclonal or monoclonal antibodies in an immunoassay for YKL-40, since both Nyirkos et al and Johansen et al teach the need for detection and quantitation of the molecule and Johansen et al specifically teach that immunoassay is one of two means by which proteins produced by different cell types can be identified, and Maurer et al teach that antibodies, both polyclonal and monoclonal, can be produced against virtually any macromolecule, and can be used in an assay for its detection, providing one of ordinary skill in the art a high expectation of success in raising the necessary antibodies and motivation for use of the antibodies in an assay.

10. Claims 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyirkos et al or Johansen et al, each in view of Maurer et al as applied to claims 9-11 above, and further in

view of Campbell (Laboratory techniques in Biochemistry and Molecular Biology, 23:1-113, 1991).

See the discussions of Nyirkos et al, Johansen et al and Maurer et al above. These references differ from the instant invention in failing to specifically teach the provision of polyclonal or monoclonal antibodies to YKL-40 and appropriate reagents in kits.

Serban et al teach a new method of immunological analysis for serum amyloid A protein (SAA) and serum amyloid P-component (SAP), kits and a method of purification of SAA and SAP. Serban et al teach that changes in concentration and ratio of acute phase proteins, e.g. CRP and SAA, and of SAP are important for diagnosis and management purposes of a number of acute and chronic inflammatory diseases such as rheumatic conditions, e.g. rheumatoid arthritis, juvenile polyarthritis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis or rheumatic fever, vasculitis syndromes, Chron's disease, autoimmune conditions, e.g. systemic lupus erythematosus or polymyositis, malignancies, transplant rejection and the like. Serban et al teach test kits containing, for example, a suitable carrier, e.g. a carrier having a plastic surface or a carrier coated with a polypeptide, polysaccharide or synthetic organic polymer bearing nitrophenyl groups, preferably trinitrophenyl groups, optionally solutions of a compound bearing nitrophenyl groups, preferably trinitrophenyl groups, solutions of a monoclonal or of polyclonal antibodies binding SAA or SAP, and, if said first antibodies are not labeled with an enzyme, solutions of polyclonal, enzyme-conjugated second antibodies binding said first antibodies, enzyme substrates in solid or dissolved form, standard solutions of SAA and/or SAP, buffer solutions and optionally calcium salts or related bivalent salts such as zinc or cupric salts in solid or dissolved form, and optionally pipettes, reaction vessels, calibration curves, color intensity tables and the like. The solutions may be in concentrated form or freeze-dried requiring dilution with water or buffer solution before use. See column 4, line 37 through column 5, line 3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the various reagents taught by Nyirkos et al, Johansen et al and Maurer et al in a kit because the use of kits has the advantages of easy storage, economy and convenience such as taught by Serban et al. A skilled artisan would have had a reasonable expectation of success in

assembling various reagents into kits because Serban et al teach that such kits can incorporate many different reagents and apparatus appropriate for performing an immunoassay, and that such kits are routine used in the art to detect various conditions including acute and chronic inflammatory diseases such as rheumatic conditions.

Conclusion

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao-Thuy Nguyen whose telephone number is (703) 308-4243. The examiner can usually be reached Monday through Wednesday, from 8:30 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bao-Thuy Nguyen
Patent Examiner
Art Unit 1641

Application No.: ~~08/~~ 09/215077

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Applicant should follow the format of the attached sample statement to request that the CRF filed in the parent application be used to create a CRF in this application.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

Sample Statement

Sample Request to Use Computer Readable Form from Another Application

The following paragraph, or language having the same effect, can be used to invoke the procedures of 37 CFR section 1.821(e) in which an identical computer readable form from another application is used in a given application. The paragraph should be incorporated into a separate paper to be submitted in the given application:

> The computer readable form in this application, 08/100,000, is identical with that filed in Application Number 07/999,999, filed March 1, 1988. In accordance with 37 CFR 1.821(e), please use the [first-filed, last-filed or only, whichever is applicable] computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence Listing is [included in the originally-filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification, whichever is applicable].